STATUS OF THE CLAIMS

Claims 1-12, 15, 21, 23-25, 27, 28, 30-36, 38-48, 51-76 are pending. Claims 41-45, 47, 48, 51-63 have been withdrawn from further consideration by the Examiner as being drawn to a non-elected invention. Claims 1-12, 15, 21, 23-25, 27, 28, 30-36, 38-40, 46, 64-76 are currently under consideration.

The application has been amended, in accordance with the Examiner's suggestion, to incorporate the nucleic acid and amino acid sequences of the III2R and H2F antibodies, both of which are disclosed in the Manheimer-Lory paper. The enclosed Amendment Under 35 C.F.R. §1.825 (a) and (b) inserts additional sequence listings into the application and this paper inserts SEQ ID NOs into the specification at the relevant points. Manheimer-Lory is cited in the specification (page 36, lines 4-20) and is incorporated by reference (page 54, lines 23-24). The amendment therefore does not constitute new matter. Applicants verify that the sequences disclosed in the Manheimer-Lory paper are the same sequences recited in this amendment. *See In re Hawkins,* 486 F.2d 569, 179 U.S.P.Q. 157 (C.C.P.A.1973).

Claims 24 and 28 have been amended herein to more particularly point out the invention. Support for the amendment is found on page 20, line 21-page 21, line 6, and page 25, line 25-page 26, line 21.

No new matter has been added by this amendment. This amendment does not narrow the scope of any claim.

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Enablement Rejection Under 35 U.S.C. § 112 First Paragraph

Claims 1-12, 15, 21, 23-25, 27, 28, 30-36, 38-40, 46, 64-76 stand rejected under 35 U.S.C. §112, first paragraph for alleged lack of enablement. The Office maintains the rejection alleging the specification fails to disclose either an appropriate biological deposit or a disclosure of the entire sequence of the recited antibodies. For the reasons put forth below Applicants submit the rejection is in error.

The 3D1 Antibody

In a Preliminary Amendment filed on August 28, 2002 Applicants submitted the entire amino acid and nucleotide sequence of 3D1 antibody thereby making the antibody available to the public. The Office has now objected to this amendment, alleging the application as filed does not provide support for the entire nucleotide and amino acid sequence. According to the Office, the specification only provides support for the sequence of the variable region. Applicants respectfully submit that the Office has misunderstood the specification.

Disclosure of the 3D1 antibody is not limited to merely the variable region, as suggested by the Office. For example, the specification states "the terms 'HF2.3D1' and '3D1' refer to murine immunoglobulin specific to B7-2. . . The terms 'immunoglobulin' or 'antibody' include whole antibodies. . . " (page 14, lines 1-4). The specification also states on page 4 lines 1-7 (emphasis added):

> In particular an embodiment of the invention is a humanized immunoglobulin which specifically binds to B7-2 and comprises a humanized light chain comprising three light chain CDRs from the mouse 3D1 antibody and a light chain variable region framework sequence from a human immunoglobulin light chain, and a humanized heavy chain

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comprising three heavy chain CDRs from the mouse 3D1 antibody and a heavy chain variable region framework sequence from a human immunoglobulin heavy chain

The term, comprising, is open ended and therefore would include portions of the 3D1 antibody outside of the variable region. The specification therefore supports the entire sequence of the antibody and Applicants respectfully submit the Office's objection is unfounded. Additionally, Applicants now submit a sequence listing of the 3D1 antibody in conformance with 35 C.F.R. §1.825(a)(b). Thus, Applicants request that the office withdraw this rejection.

The III2R and H2F Antibodies

The Office has acknowledged that Applicants never actually used the III2R or H2F antibodies in practicing the claimed invention, but rather merely relied on portions of the printed sequences to derive the claimed subject matter. The Office has also acknowledged the availability of the sequences for the III2R and H2F antibodies in the prior art. The Office, however, objects to the recitation of these antibodies in the claims because according to the Office the antibodies are essential subject matter which cannot be incorporated by reference. Without conceding the correctness of the objection, and for the sole purpose of expediting prosecution, Applicants have amended the specification herein to recite the nucleic acid and amino acid sequences of the III2R (SEQ ID NOS: 25, 27, 29, 31) and H2F (SEQ ID NOS: 26, 28, 30, 32) variable domains as disclosed in Manheimer-Lory, *J. Exp. Med.* 174:1639 (1991). In doing so, Applicants state that the sequence disclosed in Manheimer-Lory is the same sequence incorporated into the specification by amendment made herein.

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In making this amendment Applicants do not concede the correctness of the rejection. Applicants maintain the claimed invention is enabled by the specification. Applicants submit that the basis of this rejection has no merit because the Office has mischaracterized the claims. According to the Office the claims recite as "reference or starting materials" the III2R and H2F antibodies. This is incorrect. The claims only recite small portions of these antibodies (e.g. the framework region of the variable domain). Because the claims only recite the framework region of these antibodies, disclosure of the entire antibody sequence is not required to practice the claimed invention.

The sequences of the framework regions within the variable domains were known in the art and disclosed in the specification by virtue of the citation to the Manheimer-Lory paper. The sequences of these domains are short (*see* figure 2 and Manheimer-Lory already of record) and thus, could be easily synthesized without any undue experimentation. Oligonucleotide synthesis was known in the art (*See e.g.,* S. L. Beaucage and M. H. Caruthers, 1981, *Tetrahedron Lett.* 22:1859) (Courtesy Copy enclosed). Moreover, humanizing antibodies using oligonucleotide synthesis of framework and CDR regions was practiced in the art (*See e.g.*, U.S. Patent No. 5,585,089 at column 22, lines 25-35) (already of record) and more importantly, was taught in the instant specification (page 24, line 3-page 25, line 2). A skilled artisan could easily practice the claimed invention without undue experimentation based on the disclosure in the specification and the teaching of the prior art. The invention as claimed is thus enabled.

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Indefiniteness Under 35 U.S.C. § 112 Second Paragraph

The 3D1, H2F and III2R Antibodies

Claims 1-12, 15, 21, 23-25, 27, 28, 30-36, 38-40 and 64-76 stand rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. According to the Office, 3D1, H2F, and III2R are merely "laboratory designations" which do not clearly define the claimed invention. Applicants submit the rejection has no basis.

The purpose of the definiteness requirement is to inform the public of the boundaries of infringing conduct. MPEP § 2173. A fundamental principle contained in 35 U.S.C. § 112, second paragraph is that Applicants are their own lexicographers. MPEP § 2173.01 "Definiteness of claim language must be analyzed, not in a vacuum, but in light of (A) the content of the particular application disclosure; (B) the teachings of the prior art; and (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made." MPEP §2173.02 (emphasis added). When all of these factors are considered the claim terms cannot be deemed indefinite.

The content of the specification coupled with the teaching of the prior art make the terms III2R, H2F and 3D1 definite. The sequences of each one of these antibodies was known in the art. References disclosing the sequences are cited in the specification. (See *e.g.*, page 36, lines 14-17; page 17, lines 1-5). Moreover, at the Examiner's suggestion these sequences have been incorporated into the specification.

A skilled artisan reading the claims in light of the specification would understand III2R, H2F and 3D1 refer to the antibodies corresponding to the sequences disclosed

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and cited in the specification. The claim terms, therefore are not indefinite. Moreover, there is nothing of record to the substantiate the allegation that the claim terms are indefinite. The Office merely suggests that there might be other antibodies with the same name. The Office also suggests hybridomas can undergo changes resulting in "microheterogeneity." Both of these suggestions are completely unsubstantiated by the record. Applicants call upon the Examiner to cite a reference to support his position or alternatively provide an affidavit pursuant to 37 C.F.R. §1.104(d)(2). Absent such a demonstration, the claimed invention when considered in light of the specification satisfies the definiteness requirement. Applicants respectfully request withdrawal of this rejection.

Stringent Conditions

Claims 24 and 28 stand rejected as allegedly indefinite because the metes and bounds of "stringent conditions" are not allegedly defined, which in turn also renders the term "nucleic acid" indefinite. Applicants believe the term "stringent conditions" is indeed an art recognized term and thus, the claim is definite. Nonetheless, without conceding the correctness of the rejection, and for the sole purpose of expediting prosecution, claims 24 and 28 are amended herein to remove the term "stringent conditions", thus obviating the rejection. The new term "substantially identical" is defined in the specification on page 20, line 21-page 21, line 6; and further supported on page 25, line 25-page 26, line 21. Applicants request withdrawal of this rejection.

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The Rejection Under 35 U.S.C. § 103(a)

Claims 1-12, 15, 21, 23-25, 27, 28, 30-36, 38-40, 46 and 64-76 stand rejected under 35 U.S.C. §103 as being obvious and thus unpatentable over U.S. Patent No. 6,084,067 (Freeman) in view of the art recognized methods of cloning and expressing recombinant antibodies, as evidenced by U.S. Patent No. 5,585,089 (Queen) and *Antibodies: A Laboratory Manual,* Chapter 3, Cold Spring Harbor Laboratory, 1988, (Harlow and Lane Eds.) (Harlow). The Examiner alleges Freeman teaches humanized antibodies to B7-2, Queen teaches improved methods of humanizing antibodies which maintain binding affinities of at least about 10^8 M^{-1}, and Harlow teaches $10^7 M^{-1}$ is a weak affinity for an antibody. The Examiner concludes that the claimed invention is allegedly obvious in light of the prior art. Applicants respectfully traverse the rejection.

The Patent Office bears the burden of establishing the claimed invention is prima facie obvious. MPEP § 2142. The PTO has not met its burden in the instant case.

The Claimed Invention Is Not Prima Facie Obvious

MPEP § 2143 provides the standard required to establish a prima facie case of obviousness. "First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one or ordinary skill in the art, to modify the reference or to combine what the reference teaches. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references combined) must teach or suggest all the claim limitations."

The motivation to make the claimed invention and the reasonable expectation of success must both be found in the prior art, not the applicant's disclosure. *In re Vaeck,*

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947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). The references must be considered as a whole and must suggest the desireability, and thus the obviousness, of making the combination. *Hodosh v. Block Drug Col, Inc.,* 786 F.2d 1136, 1143 n.5, 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986); MPEP § 2141.

The Cited Art Does Not Teach All Of The Claim Limitations

The prior art references combined do not teach all of the claim limitations. The claims recite "a humanized immunoglobulin having binding specificity for B7-2, wherein said immunoglobulin had a binding affinity of at least about 10^7M^{-1} and. . .least one framework region containing a substitution of at least one amino acid to a corresponding amino acid in the III2R heavy chain framework region or the H2F light chain framework region." The Examiner has cited three references, Freeman, Queen, and Harlow to support the obviousness rejection. Harlow does not teach humanization of antibodies, but teaches antibodies have a wide range of affinities. Freeman suggests the possibility of making humanized B7-2 specific antibodies, but does not teach specific affinities. Queen discloses humanized antibodies with affinities greater than 10^7M^{-1} that recognize various epitopes (e.g. IL-2 receptor and various herpes virus proteins), but does not disclose B7-2 specific antibodies. None of these references disclose the III2R or H2F antibodies. Because the combined references relied on do not teach or suggest each claim limitation the office has not established prima facie that the claimed invention is prima facie obvious.

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The Cited References Fail To Provide A Reasonable Expectation of Success

Even if the skilled artisan had been aware of the III2R and H2F antibodies, he or she would have had no reasonable expectation of success in using their sequences to modify the 3D1 antibody.

The claimed invention derives the heavy chain framework from the III2R antibody and the light chain framework from the H2F antibody. The CDRs are derived from the 3D1 antibody. The Examiner has previously pointed to Freeman as disclosing the use of the 3D1 antibody against B7-2. But nothing in the Freeman or any cited reference suggested that homology existed between the 3D1 antibody and either the H2F or III2R antibodies. The Examiner is reminded the desirability and reasonable expectation of success must be found in the prior art, and not based on hindsight in light of the Applicant's disclosure. *Vaeck, supra*.

Homology between the CDR donor antibody and the frame work acceptor antibody is critical for success in the humanization process. The specification teaches: "in a preferred embodiment, the FRs of a humanized variable region having at least about 60% overall sequence identity, and preferably at least about 80% overall sequence identity, with the variable region of the nonhuman donor" (page 30, lines 13-16). The cited art also teaches the importance of homology between the donor and acceptor antibodies (*see* Queen, column 13, lines 37-41). Nothing in the art suggested the three antibodies possessed the requisite homology. Without realizing that homology existed between the III2R, H2F and 3D1 antibodies, the skilled artisan would not even contemplate using the H2F and III2R antibodies to humanize the murine 3D1.

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The art, thus provided no motivation to use the H2F or III2R antibodies and no reasonable expectation of success that the combination would be successful.

While it is true that the Office may rely on logic and sound scientific principles in support of a rejection under 35 U.S.C. §103 (*see in re Soli* 317 F.2d 941, 947, 137 U.S.P.Q. 797, 801 (C.C.P.A. 1963)), the Office must also, however, provide some evidentiary basis for the existence and meaning of the principle or logic relied on. *See In re Grose* 592 F.2d 1161, 1167, 201 U.S.P.Q. 57, 63 (C.C.P.A. 1979). There is nothing of record to indicate the Office is relying on logic or scientific principles in the instant case. Therefore, the Office has not maintained its burden of establishing the instant claimed invention is prima facie obvious.

Furthermore, the claimed invention teaches deriving the framework region for the heavy and light chains from two distinct human antibodies. None of the cited references disclose the desirability of using two different antibodies as the source of the framework regions. Instead, the cited art teaches that antibody humanization using two different antibodies as the source for the framework region was problematic. In view of this teaching, the skilled artisan would have used only one antibody source.

Queen, alone, among the references cited by the Office, addresses the problem of how to humanize an antibody. Queen states: "a 'humanized antibody' is an antibody comprising a humanized light chain and a humanized heavy chain immunoglobulin" (column 12, lines 13-15 (emphasis added). Thus, according to Queen, both heavy and light chains are required to construct a humanized immunoglobulin. Queens preferred embodiment requires the framework region of both the heavy and light chains be derived from the same antibody. Queen states: "in many cases, it may be considered

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preferable to use light and heavy chains from the same human antibody as acceptor sequences, to be sure the humanized light and heavy chains will make favorable contacts with each other. . . .The chosen human antibody will provide both light and heavy chain acceptor sequences. In practice it is often found that the human Eu antibody will serve this role," (Column 13, lines 41-56) and "normally the heavy chain and light chain from the same human antibody are chosen to provide the framework sequences, so as to reduce the possibility of incompatibility in the assembling of the two chains" (column 50, lines 60-64).

While Queen does disclose that it might be possible to use a variety of different human framework regions (column 17, lines 24-26), Queen never successfully accomplished this. Queen discloses the humanization of seven different antibodies, and in each case a single human acceptor antibody was chosen as a source for both the heavy and light chain framework region (See Examples 1-4, column 37, line 50-column 49, line 45). Thus, a skilled artisan reading Queen in light of the other references of record would conclude there was no reasonable expectation of success in attempting to humanize an antibody using different acceptor antibodies as the source for the heavy and light chain framework regions. The attempt would, at most, be merely obvious to try, which is not the proper basis for a 103 rejection. *O'Farrell,* 853 F.2d 894, 7 U.S.P.Q.2d 1673, (Fed. Cir. 1988). Because there was no reasonable expectation of success in attaining the claimed invention based upon the disclosures in the references of record, the claimed invention is not prima facie obvious. Accordingly, Applicants respectfully request withdrawal of the rejection.

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CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: February 25, 2003

By: E Stewart Mittler
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APPENDIX OF AMENDMENTS
VERSION WITH MARKINGS TO SHOW CHANGES

The specification will read as follows:

Please replace the paragraph beginning on page 36, line 4 with the following paragraph:

To retain the binding affinity of the mouse antibody in the humanized antibody, the general procedures of Queen *et al.* were followed (Queen *et al. Proc. Natl. Acad. Sci. USA* 86: 10029 (1989), U.S. Patent Nos. 5,585,089 and 5,693,762, the teachings of which are incorporated herein in their entirety). The choice of framework residues can be critical in retaining high binding affinity. In principle, a framework sequence from any human antibody can serve as the template for CDR grafting; however, it has been demonstrated that straight CDR replacement into such a framework can lead to significant loss of binding affinity to the antigen (Tempest *et al., Biotechnology* 9: 266 (1992); Shalaby *et al., J. Exp. Med.* 17: 217 (1992)). The more homologous a human antibody is to the original murine antibody, the less likely the human framework will introduce distortions into the mouse CDRs that could reduce affinity. Based on a sequence homology, III2R (SEQ ID NOS:45, 47, 49, 51) was selected to provide the framework for the humanized 3D1 heavy chain and H2F (SEQ ID NOS:46, 48, 50, 52) for the humanized 3D1 light chain variable region. ManheimerLory, A. *et al., J. Exp. Med.* 174(6):1639-52 (1991). Other highly homologous human antibody chains would also be suitable to provide the humanized antibody framework, especially kappa light

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chains from human subgroup 4 and heavy chains from human subgroup 1 as defined by Kabat.

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Claims will read as follows:

24. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

a) SEQ ID NO: 7;

b) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 8; [,]

c) the nucleic acid sequence of a nucleic acid molecule [which hybridizes to the nucleic acid molecule comprising a nucleotide sequence according] that is substantially identical to a) [or] b) or d); [under stringent conditions,] and

d) a nucleotide sequence which is the complement of the nucleotide sequence according to a) or b).

28. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

a) SEQ ID NO: 5;

b) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 6; [,]

c) the nucleic acid sequence of a nucleic acid molecule [which hybridizes to the nucleic acid molecule comprising a nucleotide sequence according] that is substantially identical to a) [or] b) or d); [under stringent conditions,] and

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d) a nucleotide sequence which is the complement of the nucleotide sequence according to a) or b).

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